THE EFFECTS OF CARDIOVASCULAR RISK FACTORS AND MILD DEPRESSIVE SYMPTOMS ON GRAY MATTER VOLUME AMONG COGNITIVELY HEALTHY OLDER ADULTS

By

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Abstract

The present study of 64 older adults (60-80 years) investigated the impact of depressive symptoms and cardiovascular risk factors (CVRFs) on gray matter volumes. Participants' depressive symptoms were measured using the Geriatric Depression Scale (GDS) and their CVRF status was determined based on the presence of obesity and hypertension. Participants underwent neuroimaging and gray matter volumes were compared using voxel-based morphometry. Higher GDS scores (greater number of symptoms endorsed) were associated with lower gray matter volumes in the right superior temporal lobe, left inferior orbitofrontal cortex, right superior frontal cortex, left insula, and bilateral angular gyri. CVRFs were associated with larger gray matter volumes in mostly posterior regions, ranging from the middle frontal gyrus to the occipital lobe. Individuals with both CVRFs present had smaller volumes in the right lingual gyrus with higher GDS scores. In contrast, higher GDS scores were associated with *larger* gray matter volumes in the right parieto-occipital region among individuals who exhibited only one CVRF. Our results show the complex interactive roles of depressive symptoms and CVRFs on gray matter volumes and support the need for future research investigating the effects of mental and physical health on the brain.

Introduction

Although prevalence of depression is lower among older adults compared to younger adults, depression in late life can have lasting impacts on physical health and even cognitive health (Fiske et al., 2009). Depression is generally associated with lower cognitive scores among older adults (McDermott, et al., 2009). For example, Keller, et al. (2017) found that the 58 individuals with non-psychotic major depressive disorder had significantly worse scores on Logical Memory, a story recall task, than their 63 healthy counterparts. Similarly, in an earlier study consisting of 220 older adult participants, Lichtenberg et al. (1995) found that higher scores – meaning more depressive symptoms were endorsed – on the Geriatric Depression Scale (GDS) were linked to lower Logical Memory and higher Dementia Rating Scale scores. Nebes et al. (2000) also found that depression was associated with lower episodic memory and visuospatial performance in 39 older adults with depression compared to the 19 controls who were matched on age (mean = 70.6 years old) and education. Further, decreased cognitive processing resources (i.e., lower working memory and slower information processing speed scores) were observed in depressed individuals and mediated the relationship between depression and lower scores on episodic memory and visuospatial functioning (Nebes et al., 2000).

Brain structure may be negatively influenced by depression as well (Koolschijn, et al., 2009). Lim et al. (2012) reported smaller cortical thickness in the rostral anterior cingulate cortex, medial orbitofrontal cortex, dorsolateral prefrontal cortex, the superior and middle temporal cortex, and the posterior cingulate cortex in addition to smaller

hippocampal volumes among 48 older adult, drug-naive individuals with late-onset depression compared to 47 healthy controls.

In contrast, certain studies have found no significant relation between depression and cognition or brain structure. In a study consisting of 259 older adults with cognitive statuses ranging from cognitively healthy to mild cognitive impairment to mild Alzheimer's disease, Yatawara et al. (2016) noted that greater severity of depressive symptoms was predictive of lower scores on cognition with a moderate effect size in the 66 individuals with mild cognitive impairment (MCI). Specifically, greater depression severity was associated with poorer mental space and flexibility, and this, in turn, was associated with lower scores on working memory, episodic memory, and non-speed-based executive functions. However, this study observed no effect of depressive symptoms on cognition among the 104 cognitively normal older adult controls or the 89 participants with mild Alzheimer's disease. Similarly, in a study of older females conducted by Koolschijn, et al. (2010), those with mild depression did not differ in brain volume or cortical thickness in the frontal cortex from non-depressed subjects. A possible explanation for this discrepancy is that these studies examined individuals with depressive symptoms rather than clinical depression, suggesting that mild depression alone may not have significant effects on the brain.

Although there are mixed effects of depression, especially mild depression on cognition among cognitively healthy adults, there is reason to believe that mild depression or the presence of a small number of depressive symptoms may negatively impact neurocognitive functioning when paired with other health issues. It is possible that health issues may leave the brain susceptible to further damage from depressive

symptoms. For example, studies have examined depression in tandem with mild cognitive impairment (Yatawara et al., 2010) and Alzheimer's disease (Lebedeva et al., 2014) and found, respectively, that depression decreased cognitive performance and brain structure (i.e., cortical thinning in the left parietal and temporal brain regions) only when these other factors were present.

There is evidence to suggest that, similar to depression, cardiovascular risk factors (CVRFs) negatively impact the brain. Kivipelto et al. (2002) analyzed data from 1,449 people between the ages of 65 and 79 years and found that CVRFs, such as high total cholesterol levels and high blood pressure were independent risk factors for dementia. In a study of 94 females, aged 52-92, Ryan and Walther (2014) determined that high body mass index, a cardiovascular risk factor and indicator of risk for obesity, was associated with lower white matter integrity which predicted lower executive functioning, memory, and visuomotor speed. In addition to cognition, CVRFs have been shown to be detrimental to brain volume. Chen et al. (2006) found that, in a study of 337 older adults aged 60-64 years old, hypertension was associated with lower gray matter volume in the right superior, bilateral medial frontal, left superior temporal and left precentral gyri in men. No differences in gray matter were found in women as a result of hypertension. Similarly, another study comprised of 255 adults with a mean age of 44.5 years reported that gray matter volumes were lower in those with type-1 diabetes (Hughes et al., 2013). Thomas and O'Brian (2008) proposed that depression may damage vascular systems, in turn affecting cognition. They also note that cardiovascular risk factors can initiate brain structure damage which can lead to late-life depression (Thomas & O'Brian, 2008). In another study of 631 individuals, the

development of CVRFs such as low high-density lipoprotein cholesterol and baseline ischemic heart disease increased with depression over a two year period (Kim et al., 2006). These results suggest that depressive symptoms and CVRFs combined may be damaging to both cognition and brain volumes.

For these reasons, we chose to test the effects of CVRFs and depressive symptoms on brain volumes. The goals of this project are 1) to examine whether number of depressive symptoms predicts brain volumes among cognitively healthy older adults even when taking into account CVRFs, and 2) to investigate whether having greater numbers of both depressive symptoms and CVRFs impacts brain volume to a greater extent than having endorsed depressive symptoms but no cardiovascular risk factors. We predicted that 1) older adults with higher GDS scores would exhibit smaller brain volumes, and 2) older adults with higher GDS scores and greater numbers of CVRFs would have smaller brain volumes than those with similar GDS scores and fewer to no CVRFs.

Method

Participants

Participants in this study were cognitively healthy older adults between the ages of 60 and 80 years (n = 64). Thirty-four females and 30 males participated in this study. Participants had an average of 16.64 years of education and were not diagnosed with mild cognitive impairment or dementia. The average number of depressive symptoms endorsed was 3.19 out of 30 possible symptoms and scores in the sample ranged from 0 - 10. Cardiovascular risk factor (CVRF) status was determined on a 0 - 2 scale.

Twenty-seven individuals endorsed zero CVRFs, 24 endorsed one, and 13 endorsed both. See Table 1 below.

Table 1. Demographics of cognitively healthy older adult participants

Sample size	n = 64
Age (years) (S.E.M.)	68.98 (0.677)
Education (years) (S.E.M.)	16.64 (0.262)
Gender (F/M)	34/30
GDS score (S.E.M.)	3.19 (0.302)
CVRF status (0,1,2)	27/24/13

Depressive symptoms

Depressive symptoms were measured using the 30-item Geriatric Depression Scale (GDS; Sheikh & Yesavage, 1986). A score of 0 - 9 is considered normal (non-depressed). All participants scored between 0 - 10 points.

Cardiovascular risk factors

A composite score was created from two CVRFs, self-reported hypertension and body mass index (BMI). BMI was calculated based on measured height and weight (BMI = kg/m^2 where kg is weight in kilograms and m^2 is height in meters squared). CVRF scores ranged from 0 - 2. BMI ≥ 25 and hypertension contributed 1 point each.

Image acquisition

Magnetic resonance imaging (MRI) brain scans were collected using a Sieman's Skyra 3T scanner. High-resolution MPRAGE images (voxel size = $1mm^3$, TR = 2300ms, TE = 2.95ms, TI = 900ms) were collected for each participant and used in the present analysis.

Image processing/analysis

Excess skull and non-brain matter were removed from images in Freesurfer. Scans were then realigned to the anterior and posterior commissure in SPM12

(Ashburner, 2010). Brain images were segmented into white matter, gray matter, and cerebrospinal fluid. We used DARTEL (Diffeomorphic Anatomical Registration using Exponentiated Lie algebra; Ashburner, 2007) to create a custom template from the segmented gray matter. We then normalized the raw gray matter images to the custom template. Images were then smoothed with a 10mm full-width-half-maximum kernel.

Multiple regressions were performed to test the effects of GDS score, CVRFs, and CVRF x GDS on brain volumes. Age, education, and ICV were included as covariates. Intracranial volume (ICV) was measured using the sum of the raw white matter, gray matter, and cerebrospinal fluid volumes.

Originally, we attempted to threshold clusters at a p-value of 0.001 with a minimum cluster size of 50, but no clusters met that threshold. Subsequently, clusters were thresholded at a p-value of 0.01 and a minimum cluster size of 10 to determine regions of interest. Marsbar (Brett et al., 2002) was used to extract a single volume measure from clusters meeting the above significance threshold by averaging across all voxels within the cluster for each participant. Volumes from regions of interest derived from the GDS x CVRF interactions were analyzed further in SPSS v. 26 to test simple effects (IBM Corp, released 2019, Armonk, NY, USA).

Results

Rgressions were performed using SPM12 in order to examine the effects of depressive symptoms (GDS score), CVRFs, and the interaction between depressive symptoms and CVRFs on gray matter volumes. Age, ICV, and education were included as covariates.

GDS score. The VBM analysis showed that higher GDS scores were associated with lower gray matter volumes in several regions, including the right superior temporal lobe, left inferior orbitofrontal cortex, right superior frontal cortex, left insula, and bilateral angular gyri (see Table 2, Figure 1a). There were no instances in which higher GDS score was associated with larger gray matter volumes.

CVRFs. The VBM analysis showed that individuals with CVRFs had larger gray matter volumes in several regions, including the left inferior temporal lobe, left lingual gyrus, left middle occipital gyrus, left cuneus, right superior occipital lobe, right postcentral gyrus, right precuneus, right precentral gyrus, right middle frontal gyrus, and bilateral superior parietal regions (see Table 2, Figure 1b). There were no instances in which the presence of CVRFs was associated with lower gray matter volumes.

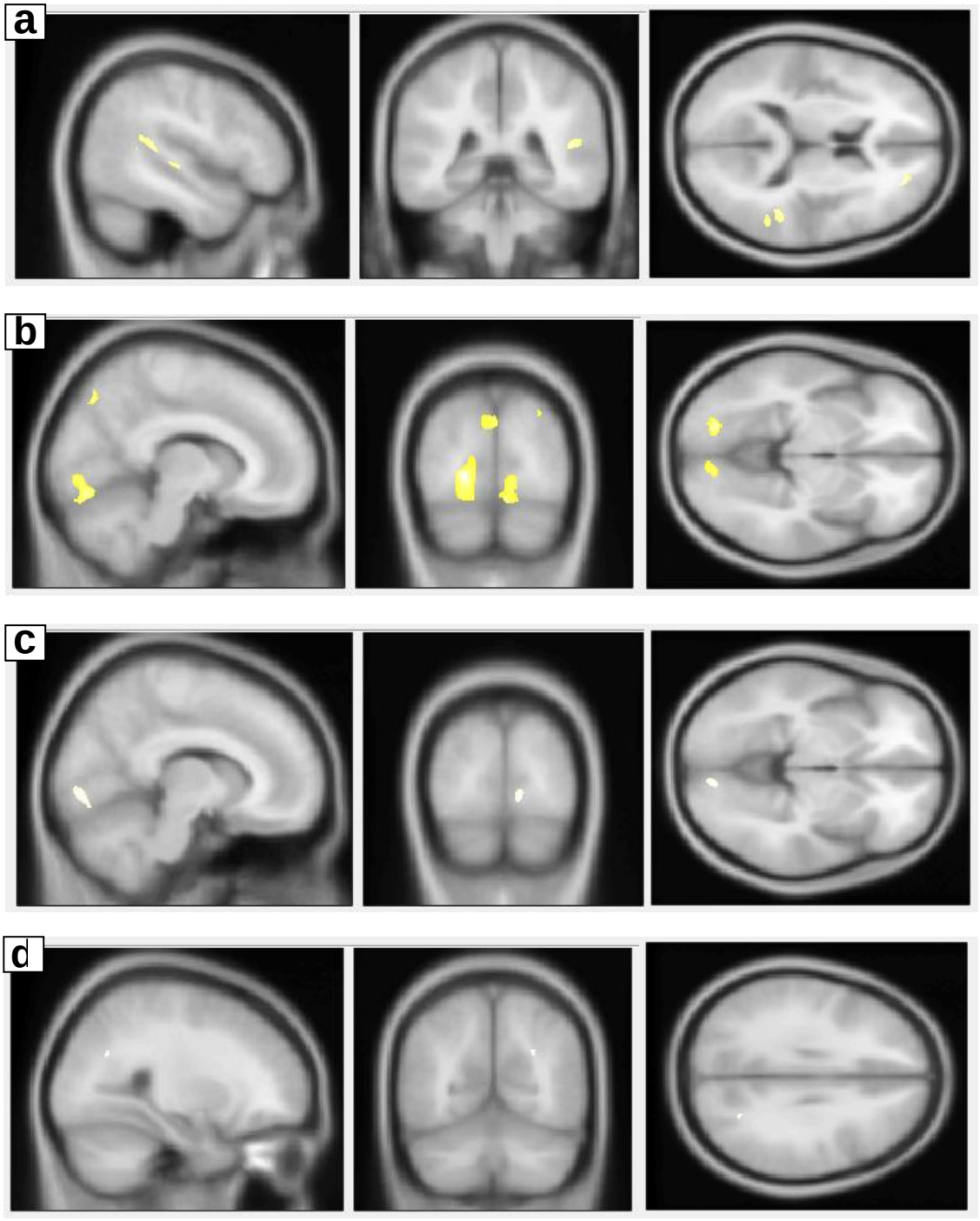

Figure 1. Significant clusters ($p < 0.01$, k = 10) for a) GDS negative associations (x,y,z coordinates: 48, -39, 13), b) CVRF positive associations (10, -82, -6), c) GDS x CVRF negative association (10, -85, -5), and d) GDS x CVRF positive association (27, -63, 29).

Table 2. Regions in which differences in volumes were detected as a function of GDS score or CVRF status, k ≥ 10, $p < 0.01$, with age, ICV, and education as covariates. The Montreal Neurological Institute (MNI) coordinates of the location of maximal significance, the *t* value, and cluster size (in mm^3) of each cluster are provided. L: left hemisphere; R: right hemisphere; GDS: Geriatric Depression Scale; CVRF: cardiovascular risk factors.

	MNI coordinates				
Region	x	y	z	*t*-value (peak intensity)	Cluster size
Gray matter regions					
GDS negative associations					
R superior temporal lobe	50	-22	0	2.66	608
	48	-39	13	2.65	656
L inferior orbitofrontal cortex	-26	35	-7	2.48	34
R superior frontal cortex	25	46	12	2.91	207
L insula	-36	-18	22	2.45	50
L angular gyrus	-36	-62	26	2.68	90
R angular gyrus	39	-58	27	2.59	193
	56	-53	31	2.54	110
CVRF positive associations					
L inferior temporal lobe	-45	-41	-26	2.53	264
L lingual gyrus	-20	-81	-2	3.29	2601
L middle occipital gyrus	-30	-77	12	2.52	41
	-37	-66	27	2.48	16
L cuneus	-1	-81	32	2.65	830
R superior occipital lobe	30	-83	38	2.70	55
R postcentral gyrus	62	-19	40	2.67	115
R precuneus	14	-75	48	3.28	796
R precentral gyrus	50	7	48	3.08	115
R middle frontal gyrus	31	24	54	3.18	454
L superior parietal	-26	-71	54	2.94	242
R superior parietal	18	-48	71	2.63	67
CVRF x GDS negative association					
R lingual gyrus	10	-85	-5	2.61	312
CVRF x GDS positive association					
R parieto-occipital	27	-63	29	2.51	38

GDS score and CVRFs. The VBM analysis showed that gray matter volumes were lower in a region of the right lingual gyrus among those with higher number of depressive symptoms and CVRFs (hypertension and BMI ≥ 25). More specifically, simple correlations indicated that individuals with both CVRFs present had marginally lower volumes as GDS score increased (r = -0.539, p = 0.057) whereas individuals with only one CVRF (r = -0.325, n.s.) or neither CVRF present (r = 0.151, n.s.) had no significant correlation between brain volume and GDS scores (see Figures 1c & 2).

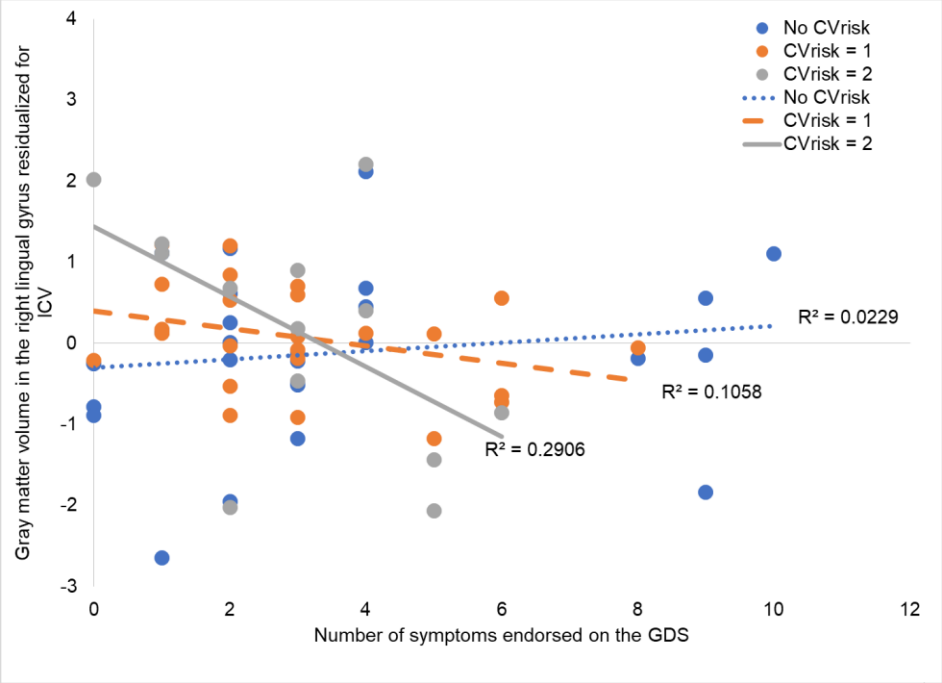

Figure 2. Pearson correlations and percent variance explained (R^2) between gray matter volume in the right lingual gyrus and Geriatric Depression Scale (GDS) score per cardiovascular risk factor (CVRF) group. The volumes displayed were residualized for intracranial volume (ICV). Among individuals with both CVRFs (hypertension and BMI ≥ 25), higher GDS score (i.e., more depressive symptoms reported) was associated with lower gray matter volume (r = -0.539, p < 0.05). There was no association between GDS score and gray matter volume in individuals with one CVRF (r = -0.325, n.s.) or with no CVRFs (r = 0.151, n.s.). Individuals with no CVRFs are represented by the dotted line and blue dots, those with one CVRF are represented by the dashed line and orange dots, and those with two CVRFs are represented by the solid line and gray dots.

Interestingly, a different pattern was observed in the right parieto-occipital region. Higher GDS score was associated with *larger* gray matter volumes in the right parieto-occipital region among individuals who exhibited only one CVRF (r = 0.410, p < 0.01). There were no significant correlations between brain volumes and GDS scores in individuals who exhibited two CVRFs (r = 0.374, n.s.) or those who did not exhibit either CVRF (r = 0.079, n.s.; see Figures 1d & 3).

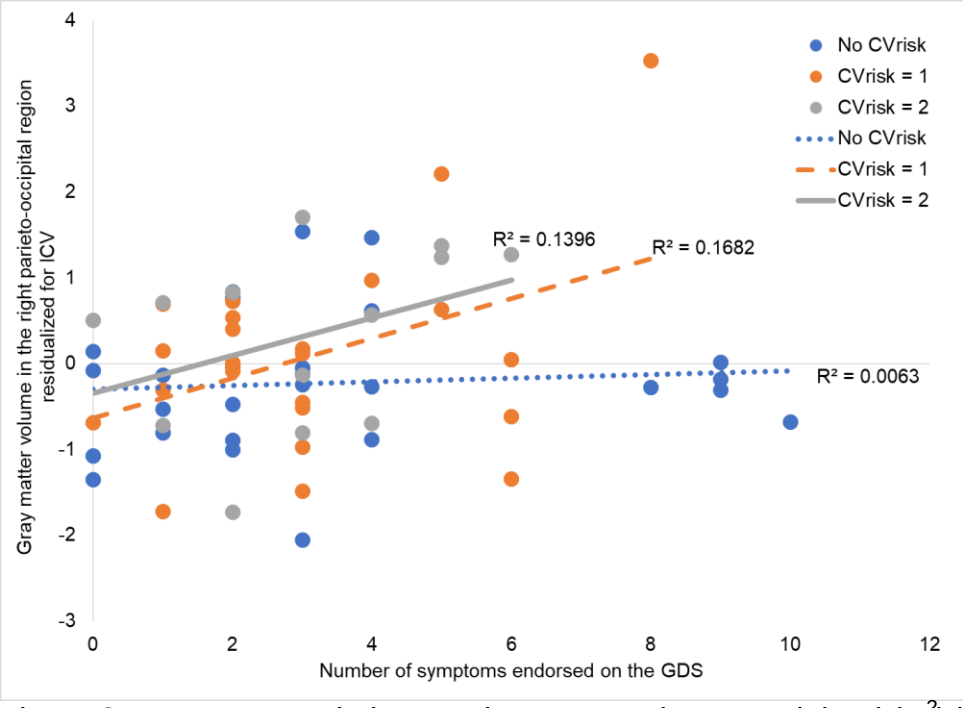

Figure 3. Pearson correlations and percent variance explained (R^2) between gray matter volume in the right parieto-occipital region and Geriatric Depression Scale (GDS) score per number of cardiovascular risk factors (CVRFs) present. The volumes displayed were residualized for intracranial volume (ICV). Among individuals with one CVRF, higher GDS scores were correlated with larger gray matter volumes in this region, (r = 0.410, p < 0.01). There were no significant associations between GDS score and gray matter volume in individuals with two CVRFs (r = 0.374, n.s.) or with no CVRFs (r = 0.079, n.s.). Individuals with no CVRFs are represented by the dotted line and blue dots, those with one CVRF are represented by the dashed line and orange dots, and those with two CVRFs are represented by the solid line and gray dots.

Discussion

The present study investigated the relationships of depressive symptoms and brain volumes among cognitively healthy older adults with varying numbers of CVRFs. First, we found that higher numbers of depressive symptoms endorsed were associated with smaller gray matter volumes in the right superior temporal lobe, left inferior orbitofrontal cortex, right superior frontal cortex, left insula, and bilateral angular gyri. Second, presence of CVRFs was associated with larger gray matter volumes in the left inferior temporal lobe, left lingual gyrus, left middle occipital gyrus, left cuneus, right superior occipital lobe, right postcentral gyrus, right precuneus, right precentral gyrus, right middle frontal gyrus, and bilateral superior parietal regions. In agreement with our hypothesis, we observed smaller gray matter volumes in the right lingual gyrus with more depressive symptoms endorsed, and this was specific to individuals with both CVRFs but not among those without CVRFs. Unexpectedly, among those who endorsed one CVRF, but not among the other groups, we found significantly larger gray matter volumes in the right parieto-occipital region with higher number of depressive symptoms endorsed.

Depressive Symptoms

The associations between depression and gray matter volumes are consistent with previous findings that show brain volumes are smaller among older adults with depression compared to individuals without depression (Koolschijn et al. 2009). Additionally, similar to Koolschijn et al. (2009) we found some associations in frontal regions of the brain (e.g., orbitofrontal cortex). It is important to note that our study examined the range of depressive symptoms expressed within older adults who were

not clinically depressed. Our results indicate that even without diagnosable major depressive disorder, depressive symptoms may still negatively impact the brain.

Cardiovascular Risk Factors

In contrast to our hypothesis, CVRFs were associated with larger gray matter volumes in several brain regions. The majority of regions showing this relationship were in the middle to posterior brain areas. The existing literature is in contrast, linking CVRFs to smaller gray matter volumes (Chen et al., 2006; Walther et al., 2010; Hughes et al., 2013) and better cardiovascular health (e.g., increased physical activity) with larger gray matter volumes (Erickson et al., 2010). However, results from a previous study have shown that developing cardiovascular risk factors after age 80 (older than the present study's average age of 68.98 years) is associated with lower risk of dementia (Corrada et al., 2017). Future studies are needed to determine if the larger gray matter volumes with CVRFs are protective to cognition.

Depressive Symptoms and Cardiovascular Risk Factor Interactions

Smaller gray matter volumes in the right lingual gyrus among those with higher number of depressive symptoms and both CVRFs is consistent with our hypothesis. A review by Thomas & O'Brian (2008) hypothesized that depression may have lasting impacts on cognition, even after remission, because it may damage vascular systems which then impact the brain. Additionally, the authors note that cardiovascular risk factors can lead to damage to brain structure which can lead to late-life depression (Thomas & O'Brian, 2008). The present study did not examine mechanisms by which depression and CVRFs interacted with each other to impact brain volumes. It is also

possible that the two risk factors (depression and CVRFs) may be impacting brain volumes by two separate mechanisms.

It is important to note that the combined impact of depressive symptoms and presence of one CVRF was associated with *larger* gray matter volumes in the right parieto-occipital region. Our findings suggest there are varied patterns of gray matter volume in different regions of the brain when both mild depressive symptoms and CVRFs are reported. Given that this pattern was not noted among individuals with two CVRFs, it may be interesting to examine whether this association holds at moderate to severe depressive symptoms or among those with three or more CVRFs.

Additional potential future directions include incorporating a wider range of depressive symptoms on the GDS and investigating whether the association between depression and lower gray matter volumes has an effect on cognition. Future studies should also explore other measures of brain health (e.g., white matter hyperintensities) which are more strongly linked to CVRFs in combination with depressive symptoms.

Conclusion

In the present study of 64 older adults, we found that depressive symptoms were associated with smaller gray matter volumes and that CVRFs were associated with larger gray matter volumes. Additionally, high GDS scores and two CVRFs were linked to smaller volumes in the right lingual gyrus whereas high GDS scores were associated with larger right parieto-occipital volumes among individuals with one CVRF. We expect that our findings will further knowledge on how mental and physical health factors influence the brain, leading to better personalized treatment for older adults.

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